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AUTHOR(S):

Sugii, Michiyasu; Okabayashi, Ichizo

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Studies on Antituberculous Compounds

Synthesis of 2,4-Disubstituted Benzoic Acids and 2,4-Disubstituted Benzaldehyde Thiosemicarbazones

Michiyasu SUGII and Ichizo OKABAYASHI*

(Ogiu Laboratory)

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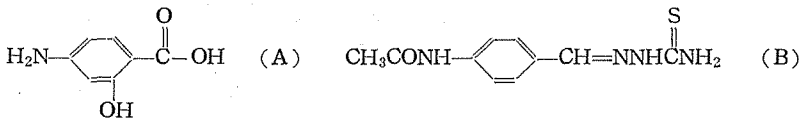
The purpose of this investigation was to synthesize 4-acetylamino-2-alkylsulfonylbenzoic acids and 4-acetylamino-2-alkylsulfonyl-benzaldehyde thiosemicarbazones and further to test their antituberculous activity.

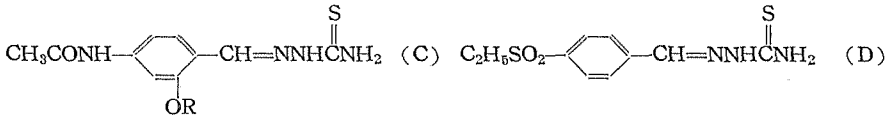
Efficacy of these compounds against Mycobacterium tuberculosis in vitro were found to be not so remarkable.

Many substances were recommended for the treatment of tuberculosis in man. In these compounds, glucoside streptomycin, as one of the series of antibiotics, *p*-aminosalicylic acid, and the thiosemicarbazone, particularly of 4-acetylaminobenzaldehyde were important.

Lean Katz[1], et al., prepared 4-acetylamino-2-alkoxybenzaldehyde thiosemicarbazones (C) as a series of compounds related to *p*-amino-salicylic acid (A) and *p*-acetylamino-benzaldehyde thiosemicarbazone (B).



(A) (B)



(C) (D)

These compounds contain an amino group in the para position to the carbon-oxygen or -nitrogen double bond. While, *p*-ethyl-sulfonylbenzaldehyde thiosemicarbazone (D), having a sulfonyl group in the similar position as above, is also efficient against Mycobacterium tuberculosis.

Considering the structure of these efficient compounds, we have synthesized 4-acetylamino-2-alkylsulfonylbenzoic acids and 4-acetylamino-2-alkylsulfonyl benzaldehyde thiosemicarbzones by the following process.

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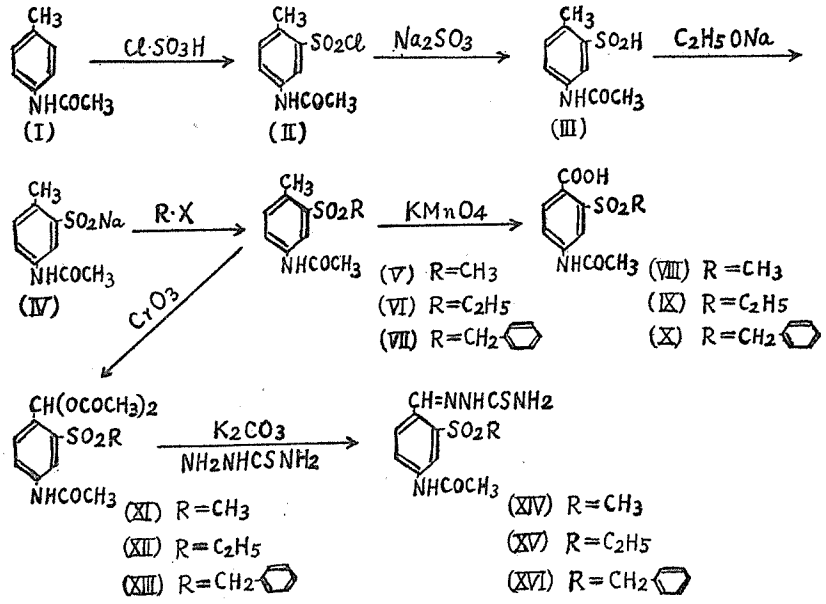
* 杉井通泰，岡林一藏



p-Acetylaminotoluene (I) was converted to 4-acetylamino-tolyl-2-sulfonyl chloride (II) using the method of Johnson[2]. The latter was reduced to 4-acetylamino-tolyl-2-sulfinic acid (III) by sodium sulfide or sodium sulfite. Sodium 4-acetylamino-tolyl-2-sulfinate (IV) was treated in alcoholic solution with alkyl halides, resulting in the corresponding 4-acetylamino-tolyl-2-alkylsulfones (V, VI, VII). Alkylsulfones (V, VI, VII) were oxidized with potassium permanganate to the corresponding 4-acetylamino-2-alkylsulfonylbenzoic acids (VIII, IX, X). Oxidation of alkylsulfones (V, VI, VII) with chromium trioxide in acetic anhydride gave the corresponding 4-acetylamino-2-alkylsulfonyl-benzaldehyde diacetates (XI, XII, XIII). The melting point of (XIII) showed 190～191° ordinarily, but sometimes a low melting product (m.p. 149～150°) was obtained. The analytical data of both compounds were identical and same thiosemicarbazone was derived from both compounds. On standing the low melting product in room temperature, it converted to the high melting compound. It has been conceivable that the former is an unstable form and the latter is a stable form.

As it had been difficult to isolate the free aldehydes from hydrolysate of the corresponding aldehyde diacetates, because of their tendency to polymerize, the diacetates were directly converted to the corresponding 4-acetylamino-2-alkylsulfonyl-benzaldehyde thiosemicarbazones (XIV, XV, XVI) with potassium carbonate and thiosemicarbazide in alcoholic solution.

Contrary to our expectation, antituberculous actions of these compounds in vitro were not so marked.

EXPERIMENTAL

Sodium 4-acetylamino-tolyl-2-sulfinate (IV). (II) was converted to (III) according to the method described in "Organic Syntheses."[3] m.p. 160° (decomp.). The mixed melting point of this substance with the compound which prepared by reducing (II) with sodium sulfide[4] showed no depression. To a hot solution of 5g. of sodium in 125cc. of absolute alcohol, was added 46g. of (III). (III) dissolved rapidly and after cooling, needles were separated. Yield, 50g. (98.5 %).

4-Acetylamino-tolyl-2-methylsulfone (V). A mixture of 23.5g. of (IV), 15g. of methyl iodide and 150cc. of alcohol was refluxed on a steam-bath for 4 hours. Alcohol was removed by distillation and water was added to the residual syrup. The precipitated crystalline product was recrystallized from methanol-water. m.p. 172°. Yield, 13g. *Anal.* Calcd. for $C_{10}H_{13}O_3NS$: N, 6.16. Found: N, 6.28.

4-Acetylamino-tolyl-2-ethylsulfone (VI). A mixture of 23.5g. of (IV), 11g. of ethyl bromide and 150cc. of alcohol was treated as described in (V). m.p. 128°, yield, 15g. *Anal.* Calcd. for $C_{11}H_{15}O_3NS$: N, 5.81. Found: N, 5.92.

4-Acetylamino-tolyl-2-benzylsulfone (VII). A mixture of 23.5g. of (IV), 13g. of benzyl chloride and 150cc. of alcohol was refluxed on a steam-bath for 4 hours. After cooling the separated crystals were filtered. Recrystallization from alcohol yielded 17.5g. of product melting at 180°. *Anal.* Calcd. for. $C_{16}H_{17}O_3NS$: N, 4.62. Found: N, 4.91.

4-Acetylamino-2-methylsulfonylbenzoic acid (VIII). A solution of 4.4g. of (V) in 180cc. of water was boiled and 12g. of potassium permanganate was added gradually to the boiling solution under stirring. After cooling, the reaction mixture was filtered and the filtrate was concentrated and acidified with hydrochloric acid. The precipitated white crystals were filtered by suction. The yield is 1.8g. After recrystallization from water, white needles, m.p. 260°, were obtained. *Anal.* Calcd. for $C_{10}H_{11}O_5NS$: C, 46.68; H, 4.31. Found: C, 46.81; H, 4.20.

4-Acetylamino-2-ethylsulfonylbenzoic acid (IX). Four grams of (VI) was boiled with 100cc. of water and 5.3g. of potassium permanganate for three hours. The reaction mixture was cooled and filtered and the filtrate was acidified with hydrochloric acid. The crystalline product was filtered, washed with water. Yield, 1.4g. Recrystallization from water yielded white crystals melting at 209~210°. *Anal.* Calcd. for $C_{11}H_{13}O_5NS$: C, 48.69; H, 4.83. Found: C, 49.10; H, 4.35.

4-Acetylamino-2-benzylsulfonylbenzoic acid (X). A 1.2l. aqueous solution of 2.4g. of (VIII) and 2.8g. of potassium permanganate was boiled for five hours. The reaction mixture was treated as described in (IX), and yielded 1.0g. of white crystals. Recrystallized from alcohol, the crystals melted at 265~266°. *Anal.* Calcd. for $C_{16}H_{15}O_5NS$: C, 57.64; H, 4.54. Found: C, 57.84; H, 4.41.

4-Acetylamino-2-methylsulfonylbenzaldehyde diacetate (XI). To 6g. of (V)

was added 60cc. of acetic anhydride. To this suspension, cooled in an ice-bath, was added dropwise 4.8cc. of concentrated sulfuric acid with stirring. The solid was dissolved. To this solution was added dropwise the solution of 7g. of chromium trioxide in 35cc. of acetic anhydride at 5~10°. After addition, the stirring was continued for thirty minutes, and the reaction mixture was poured into 600cc. of ice-water. The solution was extracted with ethyl acetate and the extract was washed with water. Ethyl acetate was removed by distillation under reduced pressure and water was added to the residual syrup, separating crystals. Yield, 5g. After recrystallization from methanol-water gave needles of diacetate, m.p. 91~93°. *Anal.* Calcd. for $C_{14}H_{17}O_7NS$: N, 4.08; Found: N, 4.15.

4-Acetylamino-2-ethylsulfonylbenzaldehyde diacetate (XII). Ten grams of (VI), 80cc. of acetic anhydride, 8.6cc. of concentrated sulfuric acid and the solution of 11g. of chromium trioxide in 55cc. of acetic anhydride were reacted and treated as described in (XI). Yield, 7.5g. After recrystallization from ethanol-water, needles, melting at 158~159°, were obtained. *Anal.* Calcd. for $C_{15}H_{19}O_7NS$: N, 3.92. Found: N, 4.03.

4-Acetylamino-2-benzylsulfonylbenzaldehyde diacetate (XIII). Seven grams of (VII), 70cc. of acetic anhydride, 5.5cc. of concentrated sulfuric acid and the solution of 6.1g. of chromium trioxide in 30cc. of acetic anhydride were reacted as described in (XI). The reaction mixture was poured into 700cc. of ice-water and allowed to stand overnight. The crystals separated were filtered and washed with water. Yield, 5.1g. After recrystallization from ethanol-water, white crystals were obtained. m.p. 190~191° (stable form), 149~150° (unstable form). *Anal* Calcd. for $C_{20}H_{21}O_7NS$: N, 3.34. Found: N, 3.30.

4-Acetylamino-2-methylsulfonylbenzaldehyde thiosemicarbazone (XIV). To a 20cc. of 80% methanol solution involving 0.4g. of (XI) were added 0.11g. of thiosemicarbazide and 0.16g. of potassium carbonate. The mixture was refluxed on a steam-bath for one hour. After cooling the crystalline product was filtered and washed with methanol and water. Pale yellow crystals, m.p. 256~258° (decomp.) were obtained. Yield, 0.28g. *Anal.* Calcd. for $C_{11}H_{14}O_3N_4S_2$: C, 42.02; H, 4.49. Found: C, 41.93; H, 4.60.

4-Acetylamino-2-ethylsulfonylbenzaldehyde thiosemicarbazone (XV). To a 30 cc. of 80% methanal solution involving 0.4g. of (XII) were added 0.1g. of thiosemicarbazide and 0.15g. of potassium carbonate. The mixture was refluxed on a steam-bath for one hour. After standing overnight the crystalline product was filtered and washed with methanol and water. Yield, 0.34g. After recrystallization from acetic acid the pure compound was obtained as pale yellow needles melting at 240~241° (decomp.). *Anal.* Calcd. of $C_{12}H_{16}O_3N_4S_2$: C, 43.88; H, 4.91. Found: C, 43.76; H, 5.18.

4-Acetylamino-2-benzylsulfonylbenzaldehyde thiosemicarbazone (XVI). To a

90cc. of 80% methanol solution involving 2.75g. of (**XIII**) were added 0.6g. of thiosemicarbazide and 0.9g. of potassium carbonate and the reaction mixture treated as described in (XIV). Yield, 1.6g. After recrystallization from acetic acid yellow needles were obtained. m.p. 255~257°. *Anal.* Calcd. for $C_{17}H_{18}O_3N_4S_2$: C, 52.29; H, 4.65. Found: C, 52.21; H, 4.88.

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